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What is the impact of diabetes mellitus on radiation induced acute proctitis after radical radiotherapy for adenocarcinoma prostate? A prospective longitudinal study

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Abstract

Background: Long-term complications of diabetes include cardiovascular disease, retinopathy, nephropathy, and neuropathy. Diabetic patients with prostate cancer could be at a high risk of radiation-induced acute proctitis following radical radiotherapy. Our aims were to analyse the incidence, severity, and duration of radiation proctitis in diabetic patients treated by radical radiotherapy and combined androgen deprivation for prostate cancer.

Material and Methods: On the bases of inclusion and exclusion criteria 716 patients with prostate cancer were retrospectively recruited. Patients were stratified into diabetic patients and non-diabetic patients. The incidence, severity, and duration of proctitis were the main outcomes. A polynomial ordered logistic regression was fitted to determine the influence of diabetes status, age, blood pressures medication, co-morbidities, Gleason score, PSA after treatment, and tumour stage on the grades of proctitis. Time to resolution per year was modelled as a negative binomial generalised linear model.

Results: The overall mean age of patients was 67.44 (SD 6.77) years with a follow-up time of 3.36 (SD 2.05) years. Data exploratory analysis suggested that the only highly significant explanatory variable was the presence or absence of diabetes. Polynomial ordered logistic regression, however, showed that the presence (or not) of diabetes remained as the only significant predictor ($t = -2.74$; $p = 0.0059$) of severity of proctitis. A negative binomial generalised linear model showed that both grade of proctitis ($z = -17.178$; $p < 0.001$), and diabetes ($z = -5.92$; $p < 0.001$), were highly significant predictors of time to resolution.

Conclusions: Diabetic patients were significantly more likely to have proctitis after radical radiation therapy for prostate cancer. Diabetes was significantly associated with an induced risk of radiation induced proctitis and also with deceleration of its resolution.

Keywords: Prostate cancer; Diabetes mellitus; Proctitis; Radiotherapy.

Introduction

Diabetes mellitus is the one of the most common endocrine diseases in Britain. Long-standing uncontrolled diabetes could lead to long-term complications, including cardiovascular disease, retinopathy, nephropathy, and neuropathy (, 1).

A series of studies (2 - 5) have investigated the impact of diabetes mellitus on radiation toxicity of several organs such as lung and prostate. In lung cancer diabetic patients are at risk to develop clinically symptomatic pneumonitis following radiation therapy (2 - 4), with no significant difference between patients who had long or short-term diabetic history (4). Recently, Zhou et al. (5) reported a significant difference in the incidence of radiation pneumonitis between diabetic and non-diabetic patients. In prostate cancer patients, a multivariate analysis identified that diabetes mellitus has a negative influence on urine incontinence and sexual function (6). One study (7) reported that high grade genitourinary toxicity was highly associated with the presence of diabetes mellitus in patients undergoing treatment of prostate cancer. Late gastrointestinal and urinary toxicities were significantly associated with diabetic patients with localized prostate cancer (8).

Despite radical radiotherapy having become a major option in the treatment of localised or locally advanced prostate cancer (9), for anatomical reasons in which the rectum is adjacent to the prostate, radiation induced injury to the rectum is still a frequent side effect of prostate cancer radiotherapy (10 -14).

The incidence of proctitis varies; several studies (15 - 17) reported that the incidence of proctitis after 3D-conformal external beam radiotherapy of localized prostate cancer constitutes between 5 - 20%. Goldner et al. (15) reported, without using any scoring system for proctitis, that 10 – 20% of patients developed rectal bleeding and proctitis. Whereas Muren et al. (16) stated that any symptoms which require medical managements were scored at least grade 2 toxicity; in which 17% of patients developed acute grade 2 toxicity. While others (18 - 22) reported that 50 - 85% of participants experience signs of proctitis include rectal discomfort, diarrhoea, urgency and rectal bleeding after pelvic radiation therapy. According to Potosky et al. (23) long period complications can comprise rectal bleeding, fistulas, stool incontinence and rectal discomfort with seldom patients required colostomy that results in significant decrements in quality of life.

Therefore, we aimed to investigate whether diabetic patients treated by neoadjuvant/adjuvant hormone therapy and radical radiation therapy for prostate cancer have higher incidence, severity and duration of radiation proctitis.

Material and Methods

This retrospective study had Caldecott Institutional Approval (Caldicott/CSAppGN021211). 716 patients underwent radical radiotherapy and neoadjuvant/adjuvant hormonal therapy were identified from comprehensive clinical databases hosted at one of main cancer centres in the United Kingdom (UK) from January 2007 to December 2013. Patients were identified from electronic databases through a validated cross linkage methodology as described previously in

detail (24, 25). Record linkage technique brings together two or more records relating to the same individual identified by a common identifier (Community Health Index [CHI] number in this series). Cross-linked databases enabled demographical and clinical data to be securely managed at one centralised database for the purpose of this study.

The database with (CHI) was linked to the following clinical systems: (i) WISDOM oncology system (Web Information System for Data Oncology Management) which securely stores the following clinical information includes clinical presentation, PSA, cancer stage, Gleason score, radiotherapy, chemotherapy, clinical complications, follow-up and mortality; (ii) Referral Management System (RMS) which is a primary care system for a population of more than 400,000 individuals. Data linkage captured the doses, start date and name of any prescribed medication (38, 39); (iii) Multidisciplinary Board Meeting (MDT) records where all patients diagnosed with prostate cancer are discussed on a weekly basis; (iv) Integrated Clinical Environment (ICE) system enhances clinicians with diagnostic services as a means to electronically order tests and view results. Using the CHI number we searched for sequential PSA results; (v) Records were searched using Clinical Portal and the In House Surgical Information System web and Technology (Insite), these databases host secure electronic patient records which systematically captures follow-up history including communication between acute and primary care.

Inclusion criteria were: (i) patients who are newly diagnosed and histologically confirmed to have localized or locally advanced adenocarcinoma of prostate; (ii) patients who acquired

primary radical radiotherapy and neoadjuvant/adjuvant hormonal therapy; (iii) patients who received a dose of radiotherapy ranged between 4500cGY – 5700cGY in 20 fraction over 20 to 32 days; and (iv) patients acquired 3D field conformal radiotherapy. Exclusion criteria were: (i) patients who received adjuvant radiotherapy following radical prostatectomy; (ii) patients with missing data including lack of the dose of radiotherapy, tumour stage, Gleason score, PSA, no history of follow-up or missing co-morbidity data (such as hypertension dyslipidaemia, cardiovascular diseases etc.); (iii) patients who had radiotherapy only; (iv) chronic proctitis; and (v) haemorrhoids.

The incidence, severity and duration of radiation induced proctitis were the primary study outcomes. Radiation induced proctitis was graded according the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) grading system of radiation proctitis in which grade 0 has no signs and symptoms and does not require medication; grade 1 has minimal side effect such as urgency, occasional pain, superficial ulceration $< 1\text{cm}^2$, mild stricture with occult rectal bleeding: treated as outpatient and does not require lifestyle adjustments; grade 2 has intermittent urgency and pain, superficial ulceration $> 1\text{cm}^2$, intermittent rectal bleeding and moderate stricture: treated as outpatient and requires lifestyle adjustments; grade 3 has persistent urgency, pain and bleeding, deep ulceration associated with severe stricture: needs hospital admission or minor surgical intervention associated radical adjustment of the lifestyle; grade 4 has severe urgency associated with severe uncontrollable pain, severe bleeding, perforation, fistula and complete

obstruction: needs hospital admission or major surgical intervention; and grade 5 has multi-organ failure, sepsis and death (26, 27).

The records were assessed for grading classification by two members of the research team (AA and CP) to rate the severity of proctitis for each patient (n=30) within the study. Inter-rater reliability between the observers was assessed using the Kappa statistic (Kappa=0.809 with $p<0.001$) and was found to have substantial agreement (28).

Patients were stratified into 2 groups, diabetic patients (group 1) and non-diabetic patients (group 2) which was identified from the same centralised database. Following exploratory analysis with simple linear models, a polynomial ordered logistic regression was fitted to determine the influence of diabetes status, age, blood pressures medication, co-morbidities, Gleason score, PSA after treatment, and tumour stage on the grades of proctitis (scored on a 0 – 5 ordinal scale). The time to resolution per year was modelled as a negative binomial generalised linear model to correct for overdispersion, with both proctitis and diabetes coded simply as present or absent.

The unresolved proctitis was defined as any patient with remaining signs and symptoms of proctitis through the whole follow-up. The probability of any individual case remaining unresolved at the end of the study was modelled as a Kaplan-Meier survival object, which was then included as the response variable in a Cox regression model, where cases remaining unresolved at the end of the study period were treated as censors. Constancy of variance in

model residuals and the normality of errors were checked for all analyses, which were conducted in **R** (version 3.2.2, **R** Core Development Team 2015).

The two groups were treated in the same cancer centre with: (1) neoadjuvant or adjuvant androgen deprivation with luteinizing hormone-related hormone analogues. In neoadjuvant / adjuvant hormonal therapy treatment begun 3 months before radical radiotherapy and was administered for a total of 6, to 24 ; (2) three field conformal radiotherapy with a median dose of 5400cGY (ranged, 4500cGY – 5700cGY), 20 fraction (ranged, 19 – 22) and 28 days (ranged, 20 – 32) following UK guidelines (UK guidelines, 29).

Results

The clinical and demographic characteristics of the study participants are shown in Table 1. The total number of patients who underwent 3D radical radiotherapy with neoadjuvant or adjuvant hormone therapy was 1046. On the bases of inclusion and exclusion criteria, 716 patients were included in this retrospective study.

The overall mean age of patients was 67.44 (standard deviation [SD] 6.77) years with a follow-up time of 3.36 (SD 2.05) years. Of 716 patients, 100 were type II diabetic and 616 non-diabetic patients. Exploratory analysis of the data suggested that the only clearly significant explanatory variable was the presence or absence of diabetes, with a marginally significant effect of blood pressure medication. Polynomial ordered logistic regression, however, showed that blood pressure medication had no significant effect ($t = -0.9001$; $p = 0.367$), and the presence (or not)

of diabetes remained as the only significant predictor ($t = -2.74$; $p = 0.0059$). A negative binomial generalised linear model also indicated that diabetes ($z = -5.92$; $p < 0.001$), was the only significant predictor of time to resolution. Model checking showed that constancy of model residuals across fitted values, and normality of errors were both satisfactory.

Cox regression of the derived Kaplan-Meier object on time to resolution, showed that only diabetic status (present or absent) was a significant predictor of time to resolution (Figure 1), and that from the beginning of the second year of observation to the end of the study, there were significant and increasing differences between diabetic and non-diabetic patients in the likelihood that their acute proctitis had been resolved. The data for diabetic and non-diabetic patients yielded an overall risk ratio of 2.02, indicating that diabetic patients were just over twice as likely, on average, to have unresolved acute proctitis.

Discussion

In the present study, we evaluated the influence of diabetes mellitus on the incidence, severity, and duration of rectal toxicity in patients with prostate cancer who underwent radical radiotherapy and neoadjuvant/adjuvant hormonal therapy. Our results identified that patients with diabetes mellitus had significantly greater rate of high grades of proctitis ($p < 0.001$). Patients without diabetes mellitus did not have an increased rate of high grades of proctitis. These findings might not be surprising, given several studies have indicated that diabetes mellitus induces radiation induced toxicity pneumonitis (2 - 5).

A series of explanations have been theorized for this association. After surgery, there has been evidence suggesting that diabetes mellitus increases morbidity and mortality rates in cancer patients (30), which could be as a consequence of reduced leukocyte activities, including chemotaxis, phagocytosis and opsonization; therefore, it affects the body innate immunity (31). Vascularity of the organ can play a major role in its tissue repair after radiotherapy: during radiation, tissue damage occurs more prominently in fast proliferating cells such as the lining epithelium of the skin and gastrointestinal tract, the blood vessels become exposed and the coagulation system also become activated leading to decrease the blood flow, thrombosis and capillary necrosis (31 - 33). In diabetic patients, the endothelial lining of the blood vessels become dysfunctional and the microvasculature impaired to dilate (31); therefore, it is expected that diabetic patients are predicted to have impairment tissue repair after radiotherapy.

Few studies (2 - 5) have investigated the impact of the pre-existing diabetes mellitus on radiation to toxicity. In lung cancer patients with pre-existing diabetic mellitus are at risk to develop clinically symptomatic pneumonitis following radiation therapy (2 - 4), but interestingly no significant difference was observed with duration of diabetic diagnosis and pneumonitis (4). In prostate cancer patients, a multivariate analysis identified that diabetes mellitus has a negative influence on urinary incontinence and sexual function (6). In keeping with our findings, (8) reported that late gastrointestinal and urinary toxicities were significantly associated with diabetic patients with localized prostate cancer treated by 3D conformal radiotherapy. Our analysis of data revealed that diabetes mellitus was significantly associated with radiation induced proctitis when compared to patients who were not diabetic. There also were significant and increasing differences between diabetic and non-diabetic patients in the likelihood that their proctitis had been resolved. The data for diabetic and non-diabetic patients yielded an overall risk ratio of 2.02, indicating that diabetic patients were just over twice as likely, on average, to have unresolved proctitis.

Time to onset of late grade 2 gastrointestinal complications was not significantly different between diabetic and non-diabetic patients, but however time to onset of genitourinary complications was statistically significant ($p=0.02$) between diabetic and non-diabetic patients (34). Our findings demonstrate that Cox regression of the derived Kaplan-Meier object on time to resolution, showed that only diabetic status (present or absent) was a significant predictor of time to resolution. These findings suggest that the existence of diabetes mellitus induce the

onset of proctitis and deaccelerate its resolution. However, other factors also might have influenced radiation proctitis such technique, including intensity-modulated radiation therapy (IMRT), and varying doses. However to the best of our knowledge, treatment of late rectal complication after IMRT has not been reported systematically and remains to be addressed in future research.

It could be questioned why this study has included the use of angiotensin converting enzyme inhibitors as a covariant factor. Our previous study (35) reported that men who were hypertensive and on angiotensin converting enzyme inhibitors and underwent radical radiotherapy for prostate cancer were significantly less likely to have radiation induced proctitis. Although the mechanism of angiotensin converting enzyme inhibitors to reduce the incidence and risk of proctitis, further work is needed fully understand the hypothesised pathways in which these factors might affect radiation induced proctitis.

All of our patients in our series has type 2 diabetes, and therefore, we were unable to explore whether there was any significant difference in the incidence of gastrointestinal and genitourinary radiotoxicity between patients taking insulin and patients who were taking antidiabetic drugs. Elsewhere however, Kalakota (7) reported that there was no difference in the incidence of gastrointestinal and genitourinary tracts toxicity between patients on insulin verse oral medications. Moreover, our study did not explore the influence of anticoagulant medication on the incidence of gastrointestinal and genitourinary tracts toxicity and this will remained to be explored in future studies.

The current study has shown that only diabetic status was a significant predictor of time to resolution, and that from the beginning of the second year of observation to the end of the study, there were significant and increasing differences between diabetic and non-diabetic patients in the likelihood that their acute proctitis had been resolved.

To date, there is no evidence which has demonstrated an association between proctitis and age, Gleason score or stage (35); and our findings reported similar data.

One of the limitations in the existing literature was the absence of the implementation of a reliable and valid method to evaluate and measure proctitis (15 - 17, 22, 36, 37). A series of studies has reported proctitis as present or absent without acknowledging its grades of severity (15 - 17). The current study has used a valid and reliable method, the EORTC and RTOG grading system to evaluate the severity of radiation induced proctitis (26, 27). This grading classification of proctitis was verified by many studies and was found to be reliable and consistent (38 - 41).

All our patients were treated by three field conformal radiotherapy with a median dose of 5400cGY (ranged, 4500cGY – 5700cGY), 20 fraction (ranged, 19 – 22) and 28 days (ranged, 20 – 32) following UK guidelines (UK guidelines, 29); therefore, it was impossible to evaluate the incidence of radiation proctitis in diabetic patients who were treated by higher or lower doses of radiation radiotherapy as this was the UK recommended dose at that time

One of the limitations of this study was a short follow-up. Further study is recommended to evaluate the incidence, severity, and duration of radiation proctitis in diabetic patients treated by radical radiotherapy and combined androgen deprivation for prostate cancer with longer follow-up.

Conclusion

Our results demonstrate that diabetic patients are more likely to have high grades of proctitis after radical radiotherapy with neoadjuvant or adjuvant hormone therapy. Diabetic patients were significantly associated with induced risk of radiation induced proctitis and also with deceleration in its resolution. Special care and risk stratification of patients with DM undergoing RT for prostate cancer should be taken into consideration in clinical management of this patient group.

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